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PROPRIETARY DRUG NAME/GENERIC DRUG NAME: Detrol® and Lyrica® / Tolterodine and Pregabalin

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: See USPI for each compound

NATIONAL CLINICAL TRIAL NUMBER: N/A

PROTOCOL NO.: A8881001

PROTOCOL TITLE: A Phase 2, 26 Week, Multicentre, Randomized Double Blind, Placebo-Controlled, Crossover Study Evaluating the Efficacy and Safety of Tolterodine, Pregabalin and a Tolterodine-Pregabalin Combination for Idiopathic Overactive Bladder

Study Centers: There were 22 centers (5 in Czech Republic, 4 in Lithuania, 3 in Norway, 4 in Slovakia, 3 in Sweden and 3 in the United Kingdom).

Study Initiation and Completion Dates: 19 December 2005 to 17 November 2006

Phase of Development: Phase 2

Study Objectives:

The study was designed to address the primary and secondary objectives.

- Primary: To assess the efficacy and safety of a standard dose antimuscarinic (tolterodine sustained release (SR) 4 mg once daily [OD])/α2δ ligand (pregabalin 150 mg twice daily [BID]) combination for the treatment of idiopathic overactive bladder (OAB) syndrome compared with standard therapy (tolterodine SR 4 mg OD)

- Secondary: To assess the efficacy and safety of an α2δ ligand (pregabalin 150 mg BID) for the treatment of idiopathic OAB syndrome compared with standard therapy (tolterodine SR 4 mg OD) and placebo

Exploratory:

- To determine potential for a synergistic effect with the combination

- To compare efficacy and safety of a low dose antimuscarinic (tolterodine SR 2 mg OD)/α2δ ligand (pregabalin 75 mg BID) combination for the treatment of idiopathic OAB syndrome with standard therapy (tolterodine SR 4 mg OD)

METHODS

Study Design: This was a randomized, double blind, placebo-controlled, 3 period crossover study with 7 phases. Each treatment period (Periods 1, 2 and 3) and washout period was 4 weeks in duration. There was a 2 week follow-up after the last treatment period (Period 3). The total study duration was 26 weeks. There were 5 treatment groups, each subject received 3 of the treatments:

A. Tolterodine SR 2 mg OD combined with pregabalin 75 mg BID (low dose combination)
B. Tolterodine SR 4 mg OD (standard therapy)
C. Placebo
D. Tolterodine SR 4 mg OD combined with pregabalin 150 mg BID (standard dose combination)
E. Pregabalin 150 mg BID

Subjects receiving pregabalin 150 mg BID received 75 mg BID for the first week of the treatment period, followed by up-titration to 150 mg BID for Weeks 2 to 4. Other treatment arms did not receive sham tapering, but received standard study drug during the first week.

During the first week of the washout period, subjects in the treatment arm with pregabalin 75 mg BID had the pregabalin dose tapered to 75 mg OD in the evening for 7 days. Any treatment arm with pregabalin 150 mg BID was reduced to pregabalin 75 mg BID for 4 days, followed by 75 mg OD in the evening for 3 days. Other dosage forms received sham tapering with placebo capsules during the first week of washout period.

Number of Subjects (planned and analysed): Planned to screen approximately 340 subjects to randomize 170. Of 217 subjects screened, 188 were randomized and 186 subjects were treated. The subject disposition by treatment group is provided in Table S1.

Diagnosis and Main Criteria for Inclusion: Women ≥18 years old with symptoms of urinary frequency (≥8 micturitions on average per 24 hours) and urgency of a minimum of 4 episodes per week (defined as a sudden and compelling desire to pass urine which was difficult to defer) as confirmed by the bladder diary completed prior to Visit 2. Both continent and incontinent patients were included, consistent with the International Continence Society (ICS) definition of OAB. Subjects had to be non-pregnant and non-lactating, and either postmenopausal, surgically sterilized, or using an appropriate method of contraception. An additional inclusion requirement was that all subjects should have mean volume voided (MVV) per micturition <300 mL as verified by the bladder diary.

Study Treatment: Study drug (3 capsules in the morning and 1 capsule in the evening approximately 12 hours apart) was taken orally with a glass of water. During the first week of the washout period, subjects in Group A had the pregabalin dose tapered to 75 mg once daily in the evening for 7 days. Any treatment arm with pregabalin 150 mg BID was reduced to pregabalin 75 mg BID for 4 days, followed by 75 mg once daily in the evening for 3 days. Other dosage forms received sham tapering with placebo capsules during the fifth week of treatment.

Efficacy Evaluations: Daily Bladder Diary: The subject completed a real time urinary diary in an outpatient setting for 5 days prior to Visits 2, 3, 4, 5, 6 and 7. Data recorded during the last continuous 96 hour period in the 5 day diary period was used to determine the diary endpoints. The diaries completed prior to visits 2, 4 and 6 served as the baseline for each period. For each diary, the subject was asked to record as discrete events: voluntary toilet voids (with volume, for 2 days), leaks and episodes of urgency (with assessment of urgency severity). For each event, subjects marked the associated level of urgency; there were 5 levels from no urgency (1) to urgency incontinence (5).

The primary endpoint MVV was calculated from diary data. Additionally, the secondary endpoints of incontinence episode frequency (IEF), urgency episode frequency (UEF), mean severity of urgency, micturition frequency and normalized micturition frequency (NMF) were also determined from the diary data. Additional secondary endpoints were Patient Perception of Bladder Condition (PPBC) and OAB-questionnaire (q) Symptom Bother Severity Scale and OAB-q short form (SF) Health Related Quality of Life (HRQL). The PPBC was a single-item, 6-point scale validated, self-administered questionnaire that asked subjects to describe their perception of their bladder condition. The OAB questionnaires were developed to assess the symptom bother and HRQL impact of OAB on subjects' lives. The subject's perception of severity of her bladder symptoms was assessed using these questionnaires at Visits 2, 3, 4, 5, 6 and 7.

Safety Evaluations: The investigators obtained information on all observed or volunteered adverse events (AEs), the severity (mild, moderate, or severe) of the events, and the investigator's opinion of the relationship to the study treatment. All serious adverse events (SAEs) were to be reported immediately to the sponsor. The routine blood laboratory safety tests were performed at Visit 1 (screening) and urinalysis and vital signs were performed at Visits 1, 2, 3, 4, 5, 6 and 7. Subjects of childbearing potential had to have confirmed negative pregnancy tests taken at Visit 1 and 2 prior to randomization. Pregnancy testing was also performed at Visits 3, 4, 5, 6, and 7. Post Void Residual (PVR) urine volume was assessed at Visits 1, 2, 3, 4, 5, 6 and 7.

Statistical Methods: The primary analyses of the efficacy endpoints were based on a restricted analysis in the full analysis set (RFAS). The change from baseline in the primary endpoint (MVV) for each subject was analysed using a mixed effects model, with subject as a random effect and period and treatment as fixed effects. Treatment effects were estimated using adjusted means and presented with 90% confidence intervals (CIs).
In order to meet the objectives of this study, the following treatment comparisons were tested:

- Primary: Assess the efficacy and safety of a standard dose combination (tolterodine SR 4 mg OD)/ (pregabalin 150 mg BID) for the treatment of idiopathic OAB syndrome compared with standard therapy (tolterodine SR 4 mg OD) - D vs. B

- Secondary: Assess the efficacy and safety of pregabalin 150 mg BID for the treatment of idiopathic OAB syndrome compared with standard therapy (tolterodine SR 4 mg OD) and placebo - E vs. B and E vs. C

- Exploratory: Determine potential for a synergistic effect with the combination - D vs. B+E and A vs. B+E.

- Exploratory: Compare efficacy and safety of a low dose combination (tolterodine SR 2 mg OD)/ (pregabalin 75 mg BID) for the treatment of idiopathic OAB syndrome with standard therapy (tolterodine SR 4 mg OD) - A vs. B

All efficacy endpoints were also summarized by treatment using the statistics: - n, arithmetic mean, standard deviation, median, minimum, maximum. Summaries were presented for baseline and Week 4 for each treatment and the change from baseline within each study period for each treatment. Relevant subgroup analyses, eg stratified by age group, were also performed for the primary endpoint. Secondary endpoints were analysed using similar methods to those described for the primary endpoint, and non-parametric analyses were performed if appropriate.

The study was powered on the primary endpoint for the primary and secondary treatment comparisons. The study was not powered for the primary endpoint for the exploratory comparisons, nor for secondary endpoints for any of the comparisons in this study.

RESULTS

Subject Disposition and Demography: The subject disposition is presented in Table S1. The data for the 2 randomized subjects who did not receive study treatment were not included in any of the subsequent listings or analyses. Therefore, the number of subjects randomized and treated is reported as 186.

Table S1. Subject Disposition

		Tolterodine SR OD 2 mg + Pregabalin 75 mg BID	Tolterodine SR 4 mg OD	Placebo	Tolterodine SR 4 mg OD+ Pregabalin 150 mg BID	Pregabalin 150 mg BID
Number (%) of Subjects						
Screened	217					
Randomized	188					
Randomized and treated	186[a]					
Treated		105	104	103	102	105
Completed		100	101	101	96	99
Discontinued		5	3	2	6	6
Analysed for Efficacy						
PPAS		89	87	98	85	94
RPPAS		89	87	98	85	94
RFAS		103	104	103	100	101
FAS		104	104	103	100	101
Analysed for Safety:						
Adverse events		105	104	103	102	105
Laboratory data		104	104	103	102	103
Safety analysis set		105	104	103	102	105

FAS = full analysis set, RFAS = restricted full analysis set, PPAS = per protocol analysis set, RPPAS = restricted per protocol analysis set, BID = twice a day, OD = once daily, SR = sustained release
[a] Two subjects were randomized but did not receive study treatment (1 subject withdrew consent, and 1 subject was lost to follow-up prior to receiving study drug).

The study discontinuations are summarized in Table S2. The most common adverse events leading to discontinuation were dizziness and headache.

Table S2. Study Discontinuations

Number of subjects (%)	Tolterodine SR OD 2 mg + Pregabalin 75 mg BID	Tolterodine SR 4 mg OD	Placebo	Tolterodine SR 4 mg OD+ Pregabalin 150 mg BID	Pregabalin 150 mg BID
Total treated	**105**	**104**	**103**	**102**	**105**
Discontinuations					
Related to study drug	3 (2.9)	2 (1.9)	1 (1.0)	3 (2.9)	5 (4.8)
Adverse event	2 (1.9)	0	1 (1.0)	3 (2.9)	5 (4.8)
Lack of efficacy	1 (1.0)	2 (1.9)	0	0	0
Not related to study drug	2 (1.9)	1 (1.0)	1 (1.0)	3 (2.9)	1 (1.0)
Adverse event	0	0	0	1 (1.0)	0
Other	0	0	0	1 (1.0)	0
Subject defaulted	2 (1.9)	1 (1.0)	1 (1.0)	1 (1.0)	1 (1.0)
Total	5 (4.8)	3 (2.9)	2 (1.9)	6 (5.9)	6 (5.7)

BID = twice a day, OD = once daily, SR = sustained release

All subjects were white females and no subject had a body mass index >40 kg/m^2. The majority of subjects were between 45 to 64 years. The mean weight ranged from 45 to 107 kg and the height ranged from 149 to 180 cm. The demographic characteristics are presented in Table S3.

Table S3. Demographic Characteristics

Number of subjects = 186	All treatments
Age (years)	
<18	0
18-44	41 (22.0)
45-64	109 (58.6)
≥65	36 (19.4)
Mean (SD)	52.9 (13.3)
Range	19-80
Body Mass Index (kg/m^2)	
Mean (SD)	27.5 (4.8)
Range	17.4-40

SD = standard deviation

Efficacy Results – Primary and secondary treatment comparisons:

Primary endpoint (MVV): The primary analysis showed statistically significant differences in the change from baseline in MVV for the standard dose combination (tolterodine SR 4 mg OD / pregabalin 150 mg BID) compared with standard therapy alone (tolterodine SR 4 mg OD) ($p<0.0001$). Pregabalin 150 mg BID also showed statistically significant differences in the change in MVV from baseline compared with both standard therapy (tolterodine SR 4 mg OD) ($p=0.005$) and with placebo ($p=0.0006$) after 4 weeks of treatment.

Secondary endpoints: Note that the study was only powered to detect treatment differences in the primary endpoint (MVV) for the primary and secondary treatment comparisons. The standard dose combination demonstrated a statistically significant difference in treatment effect compared to standard therapy alone on endpoints of micturition frequency and NMF, as well as patient perception of symptom bother and HRQL. No statistically significant difference was seen in IEF, UEF or urgency severity, or PPBC.

Pregabalin 150 mg BID demonstrated a statistically significant difference in treatment effect compared to standard therapy alone on endpoints of NMF (although not absolute or percentage micturition frequency), as well as patient perception of symptom bother. No significant difference was found for endpoints of IEF, UEF, urgency severity, HRQL or PPBC compared to standard therapy alone.

By comparison to placebo, however, pregabalin 150 mg BID demonstrated a statistically significant difference in treatment effect on endpoints of micturition frequency, NMF, and all subject reported outcome endpoints of symptom bother, HRQL and PPBC. Although the UEF endpoint was not found to be significantly different to placebo, a significant effect on

urgency severity was shown. No statistically significant difference was seen in IEF compared to placebo.

Efficacy Results – Exploratory treatment comparisons

There was no statistically significant synergistic effect of the combination based on the planned comparison of the standard dose combination (tolterodine SR 4 mg OD / pregabalin 150 mg BID) or low dose combination (tolterodine SR 2 mg OD / pregabalin 75 mg BID) compared with the combined results of tolterodine SR 4 mg OD alone plus pregabalin 150 mg BID alone.

The low dose combination (tolterodine SR 2 mg OD/ pregabalin 75 mg BID) did not demonstrate increased efficacy compared to standard therapy alone (tolterodine SR 4 mg OD). The low dose combination showed a statistically significant difference in patient perception of symptom bother compared to standard therapy, but did not reach statistical significance on any of the other endpoints of IEF, UEF, urgency severity, micturition frequency, NMF, HRQL or PPBC.

Safety Results: The number of subjects with all causality AEs was similar across all treatment groups, with 25.7 to 32.4% of subjects reporting an adverse event. The pregabalin 150 mg BID-containing treatment groups had the highest number of subjects (32.4%) with all causality AEs (34 subjects receiving treatment E, 33 receiving treatment D) as well as the highest percentage of subjects with treatment related AEs (27.6% receiving treatment E, 24.5% receiving treatment D). The majority of all causality AEs were mild to moderate in intensity. Dry mouth, the most common treatment-related AE, was reported by 7.6 to 13.7% of subjects across all treatment groups, with the highest incidence reported in subjects treated with the standard dose combination (13.7%). Dizziness was reported by 0 to 10.5% of subjects across all treatments, with the highest number in subjects receiving pregabalin 150 mg BID (10.5%).

The severe treatment-related AEs were headache (low dose combination, standard dose combination), abdominal pain upper (low dose combination), dry mouth (standard therapy alone, pregabalin 150 mg BID alone), dizziness (standard dose combination, pregabalin 150 mg BID alone), vertigo (standard dose combination), fatigue (pregabalin 150 mg BID alone), and diplopia (pregabalin 150 mg BID alone). There were no SAEs.

The most frequently occurring AEs that were reported by ≥2 subjects are summarized in Table S4.

Table S4. Frequently Reported Adverse Events

	All Causalities (Treatment Related)				
MedDRA Preferred Term	**Tolterodine SR OD 2 mg + Pregabalin 75 mg BID**	**Tolterodine SR 4 mg OD**	**Placebo**	**Tolterodine SR 4 mg OD+ Pregabalin 150 mg BID**	**Pregabalin 150 mg BID**
Dry Mouth	8 (8)	9 (9)	9 (9)	14 (14)	11 (11)
Dizziness	5 (5)	2 (2)	0 (0)	6 (6)	11 (11)
Fatigue	2 (2)	4 (4)	2 (2)	2 (1)	5 (1)
Abdominal pain upper	2 (2)	1 (1)	2 (2)	2 (1)	1 (1)
Nausea	1 (1)	0 (0)	1 (1)	2 (2)	2 (2)
Vertigo	2 (2)	0 (0)	1 (1)	2 (2)	2 (2)
Headache	1 (1)	1 (1)	1 (1)	3 (2)	3 (2)
Gastrointestinal disorder	2 (2)	1 (1)	0 (0)	1 (1)	0 (0)
Constipation	1 (1)	1 (1)	1 (1)	5 (3)	1 (1)
Somnolence	0 (0)	0 (0)	1 (1)	1 (1)	2 (2)

BID = twice a day, OD = once daily, MedDRA = Medical Dictionary for Regulatory Activities

Table S5 shows the change from baseline in PVR after 4 weeks

Table S5. Descriptive Summary of Post Void Residual Volume (mL)

PVR (mL)	**Tolterodine SR OD 2 mg + Pregabalin 75 mg BID**	**Tolterodine SR 4 mg OD**	**Placebo**	**Tolterodine SR 4 mg OD + Pregabalin 150 mg BID**	**Pregabalin 150 mg BID**
N	104	104	103	102	101
Baseline					
Mean (SD)	12.9 (17.79)	11.3 (17.74)	9.9 (20.84)	13.1 (21.33)	9.9 (18.41)
Median (Min, Max)	0.0 (0,65)	0.0 (0,93)	0.0 (0,120)	0.0 (0,97)	0.0 (0,84)
Change from Baseline					
Mean (SD)	1.4 (16.91)	-0.1 (18.45)	1.5 (18.37)	7.1 (46.53)	1.0 (12.41)
Median (Min, Max)	0.0 (-30, 94)	0.0 (-87 , 77)	0.0 (-120, 78)	0.0 (-65, 420)	0.0 (-74, 35)

BID = twice a day, OD = once daily, SR = sustained release, SD = standard deviation

CONCLUSIONS:

- The primary endpoint analysis for the primary and secondary comparisons of the RFAS showed a statistically significant increase in the change from baseline in MVV for the standard dose combination (tolterodine SR 4 mg OD / pregabalin 150 mg BID) compared to standard therapy alone and for pregabalin 150 mg BID alone compared to both placebo and standard therapy (tolterodine SR 4 mg OD).

- Although the secondary endpoint analyses were not powered for the primary and secondary comparisons, they showed the following:

    - The standard dose combination demonstrated a statistically significant difference in treatment effect compared to standard therapy alone on endpoints of frequency and NMF, as well as patient perception of symptom bother and HRQL.

    - Pregabalin 150 mg BID demonstrated a statistically significant difference in treatment effect compared to standard therapy alone on endpoints of NMF and patient perception of symptom bother.

    - Pregabalin 150 mg BID demonstrated a statistically significant difference in treatment effect compared to placebo on endpoints of frequency, NMF, urgency severity, patient perception of symptom bother, HRQL and PPBC.

- The exploratory analyses suggested no formal evidence of a synergistic effect with the combination of tolterodine and pregabalin; nor of greater efficacy with the low dose combination compared to standard therapy.

- The drug was generally well-tolerated with most of the AEs being mild to moderate in intensity. The number of subjects with all causality and treatment related AEs was similar across all treatments, with 25.7 to 32.4% of subjects reporting an AE; however the number of all causality and treatment related AEs was highest in the pregabalin 150 mg BID treatment group. A total of 22 subjects (12%) discontinued from the study, 12 of whom discontinued due to AEs. There were no SAEs or deaths reported in this study. None of the subjects experienced any clinically significant laboratory abnormalities which resulted in discontinuation.